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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/026,276	02/19/98	KENTEN J	IGN-9601

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EXAMINER
HAMUD,F

ART UNIT	PAPER NUMBER
1646	9

DATE MAILED: 04/27/99

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/026,276	KENTEN et al
Examiner	**Group Art Unit**
Fozia Hamud	1646

☒ Responsive to communication(s) filed on *Jan 11, 1999*.

☐ This action is **FINAL.**

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire *3* month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) *1-100* is/are pending in the application.

Of the above, claim(s) *76-80 and 84-100* is/are withdrawn from consideration.

☐ Claim(s) _____ is/are allowed.

☒ Claim(s) *1-75 and 81-83* is/are rejected.

☐ Claim(s) _____ is/are objected to.

☐ Claims _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.

☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

☐ The proposed drawing correction, filed on _____ is ☐approved ☐disapproved.

☐ The specification is objected to by the Examiner.

☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☐ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.

☐ received in Application No. (Series Code/Serial Number) _____.

☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of References Cited, PTO-892

☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). 4

☐ Interview Summary, PTO-413

☐ Notice of Draftsperson's Patent Drawing Review, PTO-948

☐ Notice of Informal Patent Application, PTO-152

--- SEE OFFICE ACTION ON THE FOLLOWING PAGES ---

-DETAILED ACTION

Election/Restriction

1. Applicant's election with traverse of Group I, claims 1-75 and 81-83, in Paper No. 7 is acknowledged.

Claims 76-80, and 84-100 are withdrawn from consideration by the Examiner as they are drawn to non-elected groups.

Specification

2. There are sequences presented by the entire sequences themselves in claims. It is suggested that the amino acid sequences be identified only by appropriate sequence identifier as set forth in the "sequence listing" as required by 37 CFR §1.821 (d). Applicants are requested to remove the recitation of the sequences from the claims and simply recite the SEQ ID NO. Reciting the sequences themselves is awkward, difficult and increases the possibility of printer errors.

Claim rejections-35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

3a. Claims 1-14, 16-34, 36-54, 56-71, 73-75 and 81 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for " a gonadotropin releasing hormone (GnRH) fused to ubiquitin" especially as recited in claims 81 and 83, does not reasonably provide enablement for heat shock/ ubiquitin fusion proteins fused to "all" T or B cell epitopes, self epitopes,

structural mimics of biomolecules, microbial epitopes, or heat shock/ubiquitin fusion proteins which are modified at the c-terminus to inhibit cleavage by ubiquitin-specific protease or which is postranslationally modified by the addition of fatty acids, or a ubiquitin fusion protein linking two domains of secondary structure, the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

3b. Claims 1-3, 8-10, 13- 14, 16-22, 27-30, 33-34, 36-37, 41-43, 48-50, 53-54, 56-60, 65-67, 70- 71 are rejected as not being commensurate in scope with the specification with respect to the recitation of "...a heat shock/ubiquitin fusion protein fused to epitope containing segment(s) wherein the epitopes are T/B cell epitopes or self epitopes ... wherein regions of ubiquitin link two domains of secondary structure....", what is claimed in the instant invention broadly encompasses an infinite array of heat shock/ubiquitin fusion proteins which are fused to equally limitless numbers of T/B cell epitopes or self epitopes. The specification discloses the fusion of GnRH to ubiquitin for the stimulation of a strong anti-GnRH response to suppress gamete maturation in both males and females, (page 20, lines 2-25). The specification is non-enabling for the unlimited number of heat shock/ ubiquitin fusion proteins fused to T or B cell or self epitopes, which are encompassed by the scope of the claims. No material limitations for these heat shock/ubiquitin fusion proteins have been recited in the claims, the claims encompass every conceivable structure (means) for achieving the stated property (result). The claimed invention encompasses ubiquitin fusion proteins with T/B cell or self epitopes not envisioned or described in the specification, and neither does the specification

disclose how these claimed heat shock/ubiquitin fusion proteins fused to T/B cell or self epitopes can be distinguished from each other. The specification only enables the ubiquitin protein fused to GnRH as recited in claims 15, 35, 55, 72, 81 and 83, which have specific characteristics and properties. These properties may differ structurally, chemically, physically and functionally from other known ubiquitin fusion proteins. Ubiquitin fusion proteins have many applications, such as, proteins can be fused to ubiquitin for their selective degradation, ubiquitin fusion proteins are used for the expression of heterologous proteins in host cells and immunogenic peptides are fused to ubiquitin to elicit immune responses in animals or humans. Therefore, the breadth of the instant claims encompasses all different types of ubiquitin fusion proteins which have different biological functions, applications and mechanisms of action, for example, it is possible to target the degradation of a specific enzyme to turn off an unwanted metabolic pathway by fusing it to ubiquitin. It is also possible to make large quantities of a protein of interest by fusing the genes encoding said protein to ubiquitin, express the chimeric protein and then cleave the protein from the ubiqutin. Therefore, the epitope containing segment could contain a protein to be degraded, a protein to expressed or an immunogen. The possibilities of what these epitopes might be are endless. The specification discloses only the fusion of GnRH to ubiqutin and is enabled for nothing else. By application of the factors set forth in Ex parte Forman (230 USPQ 546 (Bd. Pat. App. & Int. 1986), and reiterated in In re Wands (858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)), which include (1) quantity of experimentation, (2) guidance presented, (3) the predictability of the art, and (4) the breadth of the claims, in the instant application, the quantity of experimentation to determine which epitopes to be fused to

ubiquitin to achieve the desired biological activities which are encompassed by the scope of the claims is practically infinite and the guidance provided in the specification very little. Therefore, it would require undue experimentation to determine all the possible ubiquitin fusion proteins encompassed by the scope of these claims.

3c. With respect to claims 4-7, 23-26, 38-40, 44-47, 61-64, and 82 which recite "ubiquitin fusion protein where the C-terminus is modified, and N-terminus residue is modified to a residue other than methionine and...which is postranslationally modified by the addition of fatty acids.. And which is conjugated to an immunogenic carrier protein.", these claims broadly encompass modifications to the ubiquitin fusion protein that are not disclosed in the specification. The only modifications to the ubiquitin fusion protein disclosed in the specification is one where glycine at the c-terminus is substituted for alanine, valine or cysteine in order to inhibit cleavage of the ubiquitin fusion protein by ubiquitin-specific protease, (page 14, lines 16-31). Insertions, deletions and substitutions of a single or multiple amino acids in any region of the fusion protein can have far-reaching effects and cause disruption of the secondary or tertiary structure and would alter the physical and biological characteristics of these proteins. The specification neither discloses nor teaches any fatty acids to be added to the ubiquitin fusion protein to enhance immunogenicity and where these additions should occur. The specification is also non-enabling for the GnRH fusion protein conjugated to "all" immunogenic carrier proteins but is only enabling for the GnRH peptide fused to ubiquitin. Therefore, it would require undue experimentation to the skilled artisan to determine which

modifications to make to ubiquitin fusion protein and which fatty acids to add to obtain the desired biological activities.

3d. With respect to claims 11-12, 31-32, 51-52 and 68-69 which recite "ubiquitin fusion protein....where the epitopes are structural mimics of biomolecules or microbial epitopes...." . The breadth of these claims are way beyond what is disclosed in the specification. No where in the specification is there any disclosure of structural mimics of biomolecules or microbial epitopes. Are these structural mimics biomolecules of carbohydrate, polynucleotide, or proteins ? Are the microbial epitopes viral or bacterial epitopes? What biological activities do these structural mimics of biomolecules or microbial epitopes supposed to display? Therefore, absent any guidance from the specification of the structural mimics of biomolecules and microbial epitopes, the skilled artisan could not predict which structural mimics of biomolecules or microbial epitopes would be reasonably expected to have the desired biological activities. Since there are an infinite number of structural mimics of biomolecules and microbial epitopes, it would require undue experimentation to select the right ones to display the desired biological activities.

3c. With respect to claims 74 and 75 which recite " a DNA construct encoding... and a cell containing a DNA construct....." what is claimed in the instant invention broadly encompasses "all" nucleic acids encoding a fusion protein. While the specification discloses that a fusion protein comprising a heat shock protein fused to an epitope or epitopes in a defined manner elicits highly specific immune response when administered into an animal, (see page 5, lines 25-30) and this is the property which the fusion protein is expected to exhibit, the specification is non-enabling for the

unlimited number of nucleic acids encoding a fusion protein having this property, and which are encompassed by the scope of the claims. Claims 74 and 75 are single means claims (M.P.E.P. 2164.08(a)). In In re Hyatt, 708 F.2d 712, 218 USPQ 195 (Fed. Cir. 1983), the Courts have held that: "A single means claim, i.e. where a means recitation does not appear in combination with another recited element of means, is subject to an undue breadth rejection under 35 U.S.C. 112, first paragraph." (A single means claim which covered every conceivable means for achieving the stated purpose was held nonenabling for the scope of the claim because the specification disclosed at most only those means known to the inventor). Since no material limitations for the nucleic acid encoding the fusion protein have been recited in the claims, the claims encompass every conceivable structure (means) for achieving the stated property (result), a fact situation comparable to Hyatt. The claimed invention encompasses nucleic acids not envisioned or described in the specification, and neither does the specification disclose how these claimed nucleic acids can be distinguished from each other. Therefore, it would require undue experimentation to determine which nucleic acids encoding fusion proteins having the desired biological activity, would be encompassed by the scope of the claims.

4. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4a. Claims 1-6, 8, 15-16, 20, 22-25, 27-35, 37-38, 40, 41, 43-46, 48, 50-55, 57-58, 60-63, 65-68, 71-73 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

4b. With respect to claims 1, 3, 8, 20, 22, 27-38, 40, 41, 43, 48, 50-55, 57-58, 60, 65-68, and 71-73 are vague and indefinite for the recitation of "epitope containing segment...", the meaning of this phrase is unclear the metes and bounds of these epitope containing segments are not ascertainable. The issue here is how large should these segments be.

4c. With respect to claims 4-6, 23-25, 44-46 and 61-63 which recite ".....N-terminus residue of ubiquitin is a residue other than methionine....", these claims are vague and unclear. It is suggested that the claims be amended to recite "..... wherein the N-terminal residue of a first ubiquitin protein is modified to a residue other than methionine, and said residue is fused to the C-terminus residue of a second, unmodified ubiquitin protein...".

4d. With respect to claims 20 which recites " two or more non-contiguous epitopes", it is unclear whether the non-contiguous epitopes are attached to different sites of the ubiquitin protein or whether one is fused to the ubiquitin protein and others are fused to the first epitope.

4e. Claim 15 is indefinite because "the plurality of identical epitopes.." lacks antecedent basis.

Claims 16, 36 and 56 are indefinite because "the internal fusion sites..." lacks antecedent basis.

4f. Claims 81 and 83 are vague and indefinite. The phrase "Ubiquitin having the peptide fused via its N-terminus to the C-terminal residue of ubiquitin..." is confusing because it is unclear if "its" relates to ubiquitin or to the peptide.

4g. Claims 81 and 83 recite "a ubiquitin fusion protein comprising ubiquitin having....." it is unclear if having is open or closed language. It is suggested that the claims be amended to recite "consisting" which is closed language or "comprising" which is open language.

Claim rejections-35 USC § 102

5. The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> *(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.*

5a. Claims 1, 41 and 58 are rejected under 35 U.S.C *§ 102*(b) as being anticipated by Lussow et al (1991).

Lussow et al teach a heat shock protein (hspR65) coupled to a synthetic immunogenic peptide consisting of 40 Asn-Ala-Asn-Pro (NANP) repeats from the repetitive region of the major antigen, the circumsporozite (CS) protein that covers the external surface of the human malria parasite, (Page 2297, column 2, lines 19-28). Claims 1, 41 and 58 of the present application recite "... a heat shock protein fused to epitopes..." Therefore, the heat shock protein fused to the synthetic immunogenic peptide taught by Lussow et al reference anticipates claims 1, 41 and 58.

5b. Claims 2-3, 8, 14, 42, 43, 54, 59 and 60 are rejected under 35 U.S.C *§ 102*(e) as being anticipated by (US patent 5,851,791).

Viestra et al teach ubiquitin fusion proteins where target proteins are attached to the carboxyl terminal of a ubiquitin molecule, such as the conjugation of ubiquitin to immunogolobulins (column 13, lines 30-49, and figure 7, column 11, lines 49-55). The present invention is directed to a ubiquitin fusion protein fused to a single epitope, or two or more epitopes at a fusion site selected from the N-

terminus, the C-terminus or an internal fusion site, therefore, the ubiquitin fusion proteins taught by Viestra et al reference anticipate claims 2-3, 8, 14, 42, 43, 54, 59 and 60.

5c. Claims 10, 13, 28, 33, 37, 50, 53, 67 and 70 are rejected under 35 U.S.C *§ 102*(b) as being anticipated by Mouristen et al (March 1995).

Mouristen et al teach the attachment of one or more foreign T cell epitopes into the highly conserved self protein ubiquitin. (Bridge between Pages 6 and 7). Two different ubiquitin fusion proteins were disclosed in the reference. One ubiquitin fusion molecule contained the T cell epitope ovalbumin (OVA 325-336) and the other contained another T cell epitope HEL (50-61), the injection of these ubiquitin fusion proteins into mice elicited strong antibody response against the ubiquitin self protein. Claims 10, 13, 28, 33, 37, 50, 53, 57, 65, 67 and 70 recite ".....ubiquitin fusion protein attached to T cell epitopes and self epitopes". Thus ubiquitin fusion proteins with T cell epitopes taught by Mouristen et al anticipate claims 10, 13, 28, 33, 37, 50, 53, 57, 65, 67 and 70.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> *A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.*
> *Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the*

subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

6. Claims 15, 35, 55, 72, 81 and 83 are rejected under U.S.C. § 103 as being unpatentable over Van der zee et al (1995) in view of Vannier et al (1996).

Van der zee et al teach a gonadotropin releasing hormone-protein conjugate by means of recombinant DNA technology for the development of contraceptive vaccine for domestic animals. (See abstract). Van der zee et al disclose that gonadotropin releasing hormone (GnRH) is one of the most attractive vaccine components for immunoneutralization because it is regarded as the key regulatory peptide that controls reproduction in mammals. They describe the construction of recombinant F11 fimbraie (a carrier molecule) carrying GnRH sequences (see page 753, first paragraph). Vaccination of female rats and young bull calves with the GnRH containing fimbriae induced not only a serological but also a considerable pharmacological effects. (Page 757, lines 23-26). Van der zee et al teach that GnRH fusion will be useful in the development of a new type of contraceptive vaccine.

Vannier et al teach the expression of the extracellular domain of human follicle stimulating hormone receptor (FSHR) in E.coli as a fusion protein with ubiquitin. (See abstract). Vannier et al disclose that the immunization of mice with Ub-hFSHR allowed the preparation of high affinity antireceptor monoclonal antibodies, and it also provoked antireceptor antibodies in monkeys. The authors suggest the immunization of ub-hFSHR in humans as means of contraception in men. (See page 1365).

Therefore it would have been obvious to one of ordinary skill in the art to modify the GnRH fusion protein taught by Van der zee et al by fusing GnRH to ubiquitin as taught by Vannier et al because ubiquitin is a small highly conserved protein that is found in all eukaryotic cells and that does not induce immune response in animals. One would be motivated to fuse GnRH to ubiquitin in a defined manner to stimulate highly specific anti-GnRH immune response in animals or humans because GnRH is the key regulatory brain peptide that controls reproduction in mammals and because ubiquitin fusion would allow a simple and cost effective way of producing anti-self antibodies against GnRH.

7. Applicants have failed to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth in the Notice To Comply With The Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures (see Paper No. 5 and paper No. 8).

Compliance with the sequence rules is required.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Fozia Hamud whose telephone number is (703) 308-8896. The examiner can normally be reached on Monday-Friday from 8:00AM to 4:30PM (Eastern time).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lila Feisee, can be reached on (703) 308-2731.

Official papers filed by fax should be directed to (703) 308-4227. Faxed draft or informal communications with the examiner should be directed to (703) 308-0294. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Fozia Hamud

Patent Examiner
Art Unit 1646
April 25, 1999

PREMA MERTZ
PRIMARY EXAMINER

Application No. 08/026,276

NOTICE TO COMPLY WITH REQUIREMENTS FOR PATENT APPLICATIONS CONTAINING NUCLEOTIDE SEQUENCE AND/OR AMINO ACID SEQUENCE DISCLOSURES

The nucleotide and/or amino acid sequence disclosure contained in this application does not comply with the requirements for such a disclosure as set forth in 37 CFR 1.821 - 1.825 for the following reason(s):

☒ 1. This application clearly fails to comply with the requirements of 37 CFR 1.8: 1.825. Applicant's attention is directed to these regulations, published at 114 29, May 15, 1990 and at 55 FR 18230, May 1, 1990.

☒ 2. This application does not contain, as a separate part of the disclosure on paper copy, a "Sequence Listing" as required by 37 CFR 1.821(c).

☒ 3. A copy of the "Sequence Listing" in computer readable form has not been submitted as required by 37 CFR 1.821(e).

☐ 4. A copy of the "Sequence Listing" in computer readable form has been submitte However, the content of the computer readable form does not comply with the requirements of 37 CFR 1.822 and/or 1.823, as indicated on the attached copy of marked-up "Raw Sequence Listing."

☐ 5. The computer readable form that has been filed with this application has bee found to be damaged and/or unreadable as indicated on the attached CRF Diskette Problem Report. A substitute computer readable form must be submitted as requi by 37 CFR 1.825(d).

☐ 6. The paper copy of the "Sequence Listing" is not the same as the computer readable form of the "Sequence Listing" as required by 37 CFR 1.821(e).

☐ 7. Other: _____

Applicant must provide:

☒ An initial or substitute computer readable form (CRF) copy of the "Sequence Listing"

☒ An initial or substitute paper copy of the "Sequence Listing", as well as an amendment directing its entry into the specification

☒ A statement that the content of the paper and computer readable copies are the s and, where applicable, include no new matter, as required by 37 CFR 1.821(e) or 1.821(f) or 1.821(g) or 1.825(b) or 1.825(d)

For questions regarding compliance with these requirements, please conta

For Rules Interpretation, call (703) 308-1123
For CRF submission help, call (703) 308-4212
For PatentIn software help, call (703) 557-0400

Please return a copy of this notice with your response.